STUDIES IN EXPERIMENTAL CONGENITAL SYPHILIS AND THE TRANSFERENCE OF IMMUNITY FROM IMMUNE SYPHILITIC FEMALE RABBITS TO THEIR OFFSPRING[1]

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INTRODUCTION

In a previous study of experimental congenital syphilis (1) we found that female rabbits which became pregnant within a day or two after they had been successfully inoculated with syphilis did not transmit the infection to their offspring, even though treponemes were demonstrated by animal inoculation in their blood at the time they littered and in placentae obtained from other mothers of the same experimental group a short time before they were expected to litter. In addition, it was found that the offspring of these mothers were as susceptible to infection with syphilis as the offspring of normal mothers; and that these offspring of syphilitic mothers, reared in the laboratory, showed no developmental defects that were not also observed in the offspring of normal mothers raised at the same time under identical environmental and dietary conditions.

PROBLEM

The present experiment was undertaken in a further study of experimental congenital syphilis in the rabbit to determine (*a*) whether mothers in which the syphilitic infection was well established, i.e., was of more than 90 days duration, transmitted

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the infection to their young and (*b*) in the event that the young showed no signs of syphilitic infection, whether they were immune.

EXPERIMENTAL[2]

Twenty-five adult female rabbits and 12 adult male rabbits of mixed breeds comprised the basic experimental groups. They were divided as follows:

Group I comprised 15 females inoculated on granulating wounds on the back (2) with the Nichols' strain of *T. pallidum*. Infection of each of these animals was proved by the detection of treponemes by dark-field in serum expressed from the lesions which developed at the site of inoculation. When the infection was well established, 118 to 444 days after inoculation, the animals were caged with normal male rabbits until they became pregnant. A short time before they littered, an average of 244 days after infection, from 4 to 12.5 cc. of blood was removed from the marginal ear vein of 8 of the 15 mothers of which from 2 to 4 cc. was inoculated into one or both testes of two normal rabbits. In addition, within a short time after littering, an average of 261 days after inoculation, each mother was reinoculated on the vulva with the Nichols' virus.

Sixty-three of the 109 offspring of these 15 syphilitic mothers were used in the experiment. They were divided into three groups as follows:

Group I-A comprised 19 offspring of 7 mothers. These 19 young were either born dead, died shortly after birth, or were sacrificed when a few hours old. Their organs (liver, kidneys, heart, etc.) were removed, emulsified with normal saline, or the animal was macerated in toto in a meat grinder. The emulsions of the organs or the emulsions of the ground up young from the same mothers were pooled and 1.5 cc. of the pooled emulsions inoculated into both testes of two normal rabbits. These inoculations were performed with a 16 gauge needle in order to include in the inoculum as many particles of tissue as possible. The inoculated animals were observed for 90 days.

Group I-B comprised 13 offspring of 7 mothers. These animals were raised to maturity in the laboratory to determine whether the presence of the syphilitic infection in the mother influenced the growth or development of her young. Ten of the 13 animals survived to the end of the experiment.

Group I-C comprised 31 young (19 males and 12 females) from 14 litters. These animals were inoculated at the age of from 81 to 103 days intradermally or intratesticularly with 0.2 cc. of an emulsion of a testicular syphiloma (Nichols' strain) containing approximately 3 treponemes to each two high powered dark-fields. The intradermal inoculations were performed on the sheath, at the base of the ear, or on the upper eyelid. Twenty-eight (16 males and 12 females) of the 31 original animals survived the experiment. Gland transfers were performed on

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[2] Because of the large number of animals involved, 312, and the length of time required for the adequate observation of those in several of the experimental groups, it was necessary to perform the experiment in two stages. Approximately half of the animals of the experimental and control groups was included in each stage of the experiment.

all animals that did not develop dark-field positive lesions at the site of inoculation or subsequently failed to develop generalized lesions.

Group II comprised 10 normal mothers.[3] Their 45 offspring were divided into two groups as follows:

Group II-A comprised 15 young from 8 litters, all of which were born in the laboratory. These animals were raised to maturity in the laboratory in order to compare their development with the development of the offspring of syphilitic mothers raised under identical environmental conditions. Eleven of the 15 survived to the end of experiment.

Group II-B comprised 30 young (16 males and 14 females), the offspring of 9 mothers. These animals were inoculated at the age of 84 to 100 days in the same manner as were the animals of *Group I-C*. Gland transfers were performed on all animals which failed to develop dark-field positive lesions at the site of inoculation or subsequently failed to develop generalized lesions.

Group III comprised 12 male rabbits used as controls for establishing the infectivity of the inoculation material.

RESULTS

The pertinent information concerning the 15 syphilitic mothers is compiled in *Table I*. As shown in this table, the average duration of the syphilitic infection in these animals at the time they littered was 209 days, the extremes being 118 and 444 days. All of them, therefore, had been infected sufficiently long to have become immune. This immune state was, in a measure, indicated by our inability to reinoculate these mothers shortly after they had littered, or an average of 261 days after they had been inoculated. As is also shown in *Table I*, the blood of only 2 of the 8 mothers tested was infectious for normal rabbits.

A comparison of the results of the pregnancies of the syphilitic and normal mothers and the development of their young is presented in *Table II*. As shown in this table, there was no

[3] In order to complete the experiment it was necessary to purchase 10 normal young rabbits from a dealer. These animals were secured in two lots of 5 each and were 6 weeks old when brought into the laboratory. To facilitate presentation we have considered that each lot of 5 was from the same mother. The 8 litters born in the laboratory comprised 68 young, 35 of which survived and were included in the experiment.

With the exception of the animals born outside the laboratory, the animals of *Groups I-B* and *C* and of *Group II* remained caged with their mothers until approximately 10 weeks old. These animals were marked shortly after birth by amputation of one or more of the toes of the hind feet. This means of identification served until they were large enough for leg bands.

appreciable difference in the average size of the litters of the two groups of mothers (syphilitic mothers, 7.3 offspring per litter; normal mothers, 8.5 offspring per litter). In addition, we feel the difference in the number of offspring born dead or

TABLE I

Compilation of information concerning the immune syphilitic rabbit mothers

NUMBER OF ANIMALS	NUMBER OF LITTERS	AVERAGE DURATION OF INFECTION WHEN ANIMALS:						
		Littered	Blood transferred to normal rabbits				Reinoculations performed	
			Days	Number studied	Results		Days	Results
					Positive	Negative		
15	15	209 days (118–444)	244 (178–308)	8	2	6	261 (189–563)	All negative

TABLE II

Results of the pregnancies and the growth and development of the young of syphilitic and of normal mothers

GROUP	NUMBER OF MOTHERS	NUMBER OF LITTERS	NUMBER OF YOUNG	AVERAGE NUMBER PER LITTER	NUMBER BORN DEAD OR DYING DURING FIRST 2 WEEKS	AVERAGE WEIGHT		ANIMALS RAISED TO MATURITY				Results
						At birth	At 8 weeks of age	Total number	Number surviving	Number of litters represented	Duration of observation	
						gm.	*gm.*				*days*	
Syphilitic mothers..	15	15	109	7.3	28 (25.7%)	81.6	860.9	13	10	7	226	See text, page 356. Otherwise no abnormalities
Normal mothers..	8*	8*	68	8.5	13 (19.1%)	73.9	811.8	15	11	8	196	No abnormalities

* See footnote, page 355. These animals not included.

dying shortly after birth (25.7 per cent, syphilitic mothers; and 19.1 per cent, normal mothers) is not significant. The difference in the average weight of the young of the two groups of mothers at birth (syphilitic, 81.6 gm.; normal, 73.9 gm.) and at the end

of 8 weeks (syphilitic, 860.9 gm.; normal, 811.8 gm.) apparently indicates that the offspring of the syphilitic mothers were no different in general health from the offspring of normal mothers.

In *Table II* is shown also a comparison of the uninoculated young of the syphilitic and of normal mothers, young that were raised to maturity in the laboratory. With one exception no difference was noted in the development of the young from either source. This exception concerned 5 offspring of one of the syphilitic mothers. All of them developed a patchy alopecia of the face when about six weeks of age, an occurrence which has previously been thought (3) to be due to congenital syphilis. Shortly after this was noted, one of the 5 animals was sacrificed and an emulsion of its organs inoculated into normal animals.

TABLE III

Summary of the results of the inoculations with the organs of the offspring of syphilitic mothers

NUMBER OF YOUNG	NUMBER OF LITTERS REPRESENTED	NUMBER OF YOUNG USED THAT WERE		RESULTS
		Born dead or died shortly after birth	Sacrificed	
19*	7*	11	8	All negative

* One additional animal from another litter sacrificed and its organs transferred. See text, page 357.

These inoculations proved negative. The 4 remaining animals of this litter soon thereafter regained all their hair and 3 of them survived the remainder of the experiment. The fourth died of an intercurrent infection.

The results of the inoculation of normal rabbits with the organs of the offspring of syphilitic mothers are given in *Table III*. As shown in this table, the organs of 19 young from the litters of 7 different animals were studied. These inoculations were negative in every instance. It is important to point out that 11 of these 19 young used were either born dead or died shortly after birth. Since these two occurrences have been ascribed to congenital syphilis (4) in the rabbit, this finding is very significant. In addition, the animals that were sacrificed were those

which appeared so unhealthy they were judged unlikely to survive the experiment. In every instance, therefore, organs inoculated into normal animals were from animals thought most likely to harbor the infection.

In *Table IV* are shown the results of the inoculation with syphilis of the offspring of the immune and normal female rabbits. Both groups of animals were of approximately the same age when inoculated and, as shown in *Table IV*, there was no appreciable difference between the two groups in their susceptibility to infection (offspring of syphilitic 85.7 per cent successfully inoculated, offspring of normal mothers 82.8 per cent successfully

TABLE IV

Results of the inoculation with syphilis of the young of the immune syphilitic and of normal mothers

GROUP	NUMBER INOCULATED	NUMBER OF LITTERS REPRESENTED	AVERAGE AGE WHEN INOCULATED	NUMBER SURVIVING EXPERIMENT	RESULTS		
					Positive		Negative
					Number	Infected without primary lesion	Number
			days				
Offspring of syphilitic mothers...	31	14	95	28	24 (85.7%)	4 (16.6%)	4 (14.3%)
Offspring of normal mothers....	30	9	89	29	24 (82.8%)	7 (29.2%)	5 (17.2%)

inoculated). If the incidence of infection without the occurrence of a primary lesion can be taken as an index of resistance to infection, the young of the normal mothers were more refractory to inoculation than were the young of the syphilitic mothers (29.2 per cent without primary lesions in contrast to 16.6 per cent). However, this difference is probably not significant (*Table IV*).

The fate of 29 offspring of syphilitic mothers and 20 offspring of normal mothers, the remaining young not otherwise accounted for in the experiment, is not indicated in the compilations of *Tables II–IV*. These 49 animals survived the first weeks of

life but either met accidental deaths or died of intercurrent infections before they could be utilized in the experiment. The frequency of these accidents was equally distributed between both groups of young.

DISCUSSION

The results of our experiments indicate that syphilis is not transmitted by the female rabbit to her offspring. As we have pointed out in a previous communication (1), with one exception, the observation of a single rabbit by Gregoriew (4), our results are in agreement with the findings of others who have used comparable experimental methods[4] in the study of this problem (5, 6). Gregoriew inoculated a single female rabbit in the anterior chamber of the eye. This animal littered several times thereafter, all the animals of these litters being either born dead or dying shortly after birth. Eventually two young from a litter born 90 days after the mother was infected survived and were studied. These animals both developed corneal lesions. Treponemes were demonstrated in the cornea of one of them by silver staining, and in the organs of the other by animal inoculation. Gregoriew concluded from these findings that syphilis was transmitted by infected female rabbits to their offspring and that it was responsible for the non-viability of their young. Without being able to explain Gregoriew's findings in this one animal, we feel that there is very little evidence to support either of his contentions. Our studies[5] of the transmission of the syphilitic infection from female rabbits to their offspring include the results of the inoculation of normal rabbits with the organs of 67 young from 20 different mothers. Not a single one of these inoculations was positive. The significance of these negative results is enhanced by our use as inocula of the organs of non-viable young and of young so marasmic they were not

[4] Uhlenhuth and Mulzer (7) and Truffi (8) have demonstrated the infectiousness of the organs of fetuses within a short time following the intravenous inoculation of the mother with huge numbers of treponemes. This experimental procedure, in our opinion, invalidates their results (1).

[5] The results of the present experiment and one previously reported (1).

expected to survive the experiment. We believe, consequently, that the syphilitic female rabbit seldom if ever transmits the infection to her young.

Our experiences do not support the impression of Brown and Pearce (3) and the contentions of Gregoriew and Jarisheva (9) that the presence of the syphilitic infection in female rabbits may be responsible either directly or indirectly for developmental abnormalities of their young. With one exception we observed no differences in the development of 23[5] offspring of 11 syphilitic mothers and the development of approximately the same number of young from normal mothers raised to maturity under identical environmental conditions. The one exception was encountered in the litter of a syphilitic mother, all the members of which developed an abnormal loss of hair. Normal rabbits inoculated with the organs of one of these animals were not infected. The remaining members of the litter shortly regained the lost hair and thereafter developed normally.

The factor or factors which prevent the transmission of the syphilitic infection from female rabbits to their offspring are not apparent. We assumed, as a result of our first experiment, that the placenta was responsible either by filtering out or destroying the treponemes before they reached the fetus. This assumption was predicated on the fact that in this experiment impregnation and infection coincided and therefore the placenta was sufficiently developed to form a probable barrier to the infection by the time the treponemes were in the blood of the mother in appreciable numbers. Further support of this assumption is the known difference in the histology of the placenta of rabbits (10) and of man (11). We felt that these differences permit one to assume that the placenta of the rabbit is probably a more effective barrier against the passage of the treponeme than is the human placenta. The results of later experiments, the one just presented and others not as yet completed, do not support this assumption. In these experiments the infection was well established in the females at the time they became pregnant. Under these conditions it is evident that there was abundant opportunity for infection of the embryo before the placenta

developed. It is possible that some measure of protection to the fetus may result from the manner in which the fertilized rabbit ovum is received by the uterus. In contrast to man, it does not bury itself in the uterine mucosa, but attaches itself to the surface of the decidua (12). However, since contact with the maternal circulation is soon established, it is not evident how such protection could be effective except for a very short interval.

It is possible that treponemes invade the fetus but are destroyed before the infection becomes established. The results of our first experiment do not support this assumption. In this experiment infection and impregnation occurred simultaneously and the fetal organs used for the inoculation of normal rabbits were obtained from 3 to 5 days before the termination of pregnancy. One would expect, therefore, if this assumption is correct, to find treponemes in the fetal circulation at the time these inoculations were performed. While the blood of the mothers was always infectious, the organs of their offspring were noninfectious for normal rabbits in every instance. In view of the known pathogenicity of the Nichols' strain for rabbits, it seems highly improbable that invasion of the fetus could occur frequently and under the conditions of this experiment always escape detection. Furthermore, if one accepts this assumption, one must also assume the presence in the fetus of a protective substance at least as actively treponemicidal as the arsphenamines. Should such a substance exist, it completely disappears by the eighth week of extrauterine life.

Since the offspring of female rabbits with late syphilis escape infection, it is not an unlikely assumption that they might share in the mother's immunity. Our findings, which fail to support this assumption, are not altogether expected since transference of immunity from mother to young either through the placenta or in the colostrum has been shown to occur in other infections, both in animals and in human beings. It has been shown experimentally, for example, that the young of anthrax infected ewes are more resistance to infection with anthrax than the young of normal ewes (13). It has also been shown that vac-

cinial immunity can be transferred from the sow to her pigs (14) and that under certain experimental conditions diphtheria antitoxin can be demonstrated in the blood of the young of immunized female rabbits (15, 16). In a series of similar experiments, Fraser (17) demonstrated the presence of diphtheria antibodies both in the eggs and the young of ducks immunized to diphtheria. In man passive immunity to both diphtheria and tetanus (18, 19) has been demonstrated in the young of mothers immunized during pregnancy. In addition, it has been suggested (20, 21) that the unreliability of the results of the vaccination of infants might possibly be due to the transmission of small quantities of antivirus from the mother. While the rabbit's immunity to syphilis is not nearly as absolute as the immunity of rabbits and other animals to the diseases mentioned above, nevertheless it is not unreasonable to expect occasional evidence of its transmission from immune mothers to their young. Our failure to demonstrate such an occurrence might possibly be due to the late age at which the young rabbits were inoculated. It has been shown that the immunity transferred by the female to her offspring is of short duration. It is therefore possible that had we inoculated the young of syphilitic mothers at an earlier age we might possibly have detected evidence of their resistance to infection.

CONCLUSIONS

In a study of experimental congenital syphilis in the rabbit, it was found that (*a*) female rabbits with syphilis do not transmit their infection to their offspring, (*b*) the presence of the syphilitic infection in the mother does not influence the growth or development of her young, and (*c*) the offspring of immune female rabbits were as susceptible to infection with syphilis as were offspring of normal rabbits.

Thanks are due Dr. Clarence Shaw for his assistance in the latter part of the experiment.

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DISCUSSION

DR. JOHN H. STOKES, *Philadelphia, Pa.:* I have a number of questions. Of course, for an experienced experimentalist like Dr. Kemp, I am sure these points have been covered, and it is very possible I might have missed a statement in his delivered address which covered these points. However, I wonder whether the pooling of the organ hash might have diminished the likelihood of picking out an individual animal here and there which might have been infected. I should also like to know what account was taken of the seasonal factor in the inoculation of the rabbits? Dr. Kemp might have mentioned this in his paper but I would like to hear about it at this point.

DR. THEODORE CORNBLEET, *Chicago, Illinois:* I would like to ask whether any studies have been made on the post mortem changes. This is along the same line as Dr. Stokes' question. We know that the post mortem changes vary in different organs, being more rapid, for instance, in the muscle and liver. I wonder if this has any influence on the results?

DR. IRA LEO SCHAMBERG, *Baltimore, Md.:* This curious inability of the female rabbit to transmit syphilis to her offspring, which Dr. Kemp has demonstrated, may be explicable by the great susceptibility of the *Treponema pallidum* to heat. *In vitro*, the thermal death time of the *Treponema pallidum* is 2 hours at 40–41°C. (104–105°F.), and treponomes are killed *in vivo* in this same low temperature range.

The normal rectal temperature of the rabbit is 101–103°F., and it has been demonstrated by thermocouple determinations that the temperature of the liver is considerably higher. Although the temperature of the rabbit fetus in utero has not been studied, it is probable that it is even higher than that of the internal viscera, because of its insulating jacket of amniotic fluid and its independent and circumscribed blood flow.

The presence of virulent *Treponema pallidum* in the liver and spleen of syphilitic rabbits, as well as in the placenta, as Dr. Kemp has described, may be due to the cooling of these organs by the constant flow of blood, or the treponemes may even be carried by the blood stream to these viscera from a more peripheral and cooler part. Additional suggestive evidence for the importance of a thermal factor lies in the fact that syphilitic hepatic lesions are not seen in the rabbit, even though virulent treponemes can be demonstrated in the liver by transfer to the testis of a normal rabbit.

Hence, it may be suggested that congenital syphilis does not occur in the rabbit because the *Treponema pallidum* is unable to multiply and produce lesions, and is even unable to survive, at the high temperature of the fetus in utero.

DR. I. J. ARNSSON, *Buffalo, New York:* I would like to ask the question of how many series of animals were used in the gland transplantation? We do know that the first series might be negative, but the glands of that series, if injected into a second series, might still produce positive results.

DR. JAROLD E. KEMP, *Chicago, Illinois:* In reply to Dr. Stokes' questions: (1) We practically close the laboratory in the summertime and do not attempt important experimental studies. (2) Sixty-seven young from twenty different litters were emulsified and inoculated into normal rabbits. The emulsions of the organs of the young from the same mother were pooled. These emulsions averaged approximately 50 c.c. each, 6 c.c. of which was inoculated into normal rabbits.

DR. JOHN H. STOKES: That is what I meant. If you pool six fetuses, you have a dilution of one to six right there. Suppose only one had been infected?

DR. KEMP: Since we used the Nichols' strain exclusively throughout the experiment, we feel that this experimental procedure would permit the detection of syphilis in a litter even if only one member of it were infected.

In answer to Dr. Cornbleet, the tissue of syphilitic rabbits remains infectious for normal rabbits for many hours after the death of the animal, provided it is not allowed to dry. Rosahn has shown that if such tissue is kept in the icebox it remains infectious for seven days. I do not know the extent to which post mortem changes in infected tissues influences the viability of treponemes. We did not use the organs of young in which such changes were advanced.

In regard to Dr. Schamberg's remarks, I do not believe the temperature of the contents of the pregnant uterus of the rabbit has ever been determined. If we assume that the temperature of the fetus is high enough to prevent infection, we must also assume a temperature in these tissues of at least 107.6°F., the thermal death point of the treponeme.

In answer to Dr. Arnsson, we did not feel that a series of node transfers was necessary. The Nichols' strain of treponemes is highly pathogenic for rabbits. We believed, therefore, that in this experiment we could safely assume that an animal had escaped infection provided (1) no lesion developed at the site of inoculation, (2) there was no evidence of infection without the development of a primary lesion as evidenced by the development of generalized lesions, and (3) the popliteal lymph nodes were non-infectious for normal animals.